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ANDERSEN–TAWIL SYNDROME: REPORT OF 3 NOVEL MUTATIONS AND HIGH RISK OF SYMPTOMATIC CARDIAC INVOLVEMENT

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ABSTRACT: *Introduction:* Andersen–Tawil syndrome (ATS) is a potassium channelopathy affecting cardiac and skeletal muscle. Periodic paralysis is a presenting symptom in some patients, whereas, in others, symptomatic arrhythmias or prolongation of QT in echocardiographic recordings will lead to diagnosis of ATS. Striking intrafamilial variability of expression of *KCNJ2* mutations and rarity of the syndrome may lead to misdiagnosis. *Methods:* We report 15 patients from 8 Polish families with ATS, including 3 with novel *KCNJ2* mutations. *Results:* All patients had dysmorphic features; periodic paralysis affected males more frequently than females (80% vs. 20%), and most attacks were normokalemic. Two patients (with T75M and T309I mutations) had aborted sudden cardiac death. An implantable cardioverter-defibrillator was utilized in 40% of cases. *Conclusions: KCNJ2* mutations cause a variable phenotype, with dysmorphic features seen in all patients studied, a high penetrance of periodic paralysis in males and ventricular arrhythmia with a risk of sudden cardiac death.

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Andersen–Tawil syndrome [ATS; Online Mendelian Inheritance in Man (OMIM) 170390, http://omim.org/entry/170390; Orphanet (European website providing information about orphan drugs and rare diseases) number: ORPHA37553] is an autosomal dominant potassium channelopathy caused by mutations of the *KCNJ2* gene on chromosome 17.[1] *KCNJ2* encodes the α-subunit of the inward-rectifier potassium channel Kir2.1 and is expressed in both skeletal and cardiac muscle. *KCNJ2* mutations have been shown to cause dominant-negative suppression of channel function.[2] Clinically, this leads to periodic paralysis (PP) and polymorphic ventricular arrhythmias and/or echocardiographic (ECG) abnormalities with a prolonged corrected QT (QTc) interval and a distinct U wave with long QTU interval. Most patients also have dysmorphic features, such as hypertelorism, small chin, cleft palate, clindactyly, syndactyly, or short stature.[2–6] ATS symptoms vary even within families. Mutations are highly penetrant, but expression is quite variable. The phenotypic variability and rarity of ATS make it challenging to diagnose. The disease is rare, with an estimated prevalence of 1 case per 1,000,000 population (approximately 38 cases in Poland). In England, the prevalence of genetically confirmed ATS is 0.08 per 100,000.[7] We describe the genotype–phenotype characteristics of 15 patients from 8 unrelated families with genetically confirmed ATS, including 3 with novel mutations.

METHODS

We performed a retrospective analysis of medical records of 15 Caucasian subjects (10 females and 5 males) from 8 unrelated families seen at a single neurological department during the period from January 1, 2003 through March 30, 2013. All probands were children and met the diagnostic criteria for ATS.[2–5] The mother in the family (number 6), with a history of cardiac arrhythmia, was not available for clinical and genetic studies. All subjects participated in the study after giving informed consent. The investigation was approved by the ethics committee at the Medical University of Warsaw (AKBE/80/13). Clinical evaluation included family and medical history, with review of previous medical records if applicable. Neurological and general physical examinations were performed. Serum electrolytes, both during PP episodes and interictally, and thyroid hormone

Abbreviations: ATS, Andersen–Tawil syndrome; ACC, American College of Cardiology; AHA, American Heart Association; BVT, bidirectional ventricular tachycardia; CACNA1S, calcium channel, voltage-dependent, L type, alpha 1S subunit; ECG, electrocardiography; ESC, European Society of Cardiology; ICD, implantable cardioverter-defibrillator; KCNJ2, potassium inward-rectifying channel, subfamily J, member 2; LQT7, long QT syndrome 7; NHLBI, National Heart, Lung, and Blood Institute; OMIM, Online Mendelian Inheritance in Man; ORPHA, Orphanet numerical classification of rare diseases; PP, periodic paralysis; SCN4A, sodium channel, voltage-gated, type IV, alpha subunit; SCD, sudden cardiac death; VPB, ventricular premature beat; VT, ventricular tachycardia

Key words: channelopathy; *KCNJ2*; long QT; periodic paralysis; ventricular arrhythmia

The authors dedicate this work to the late Prof. Hubert Kwiecinski, colleague and friend.

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Table 1. Clinical characteristics of ATS patients.

Patient	Mutation KCNJ2	Age at Dx (y)	Age (y) of first symptoms	PP (onset)	Cardiac manifestation onset	Maximum QTc/QTUc ms24-h ECG monitoring
1-1F	G146R	10	7 (PP)	Yes (7 y)	Asymptomatic (8 y)	QTc = 420, QTUc = 710, VPBs 6637, nsBVT 5
1–2F	G146R	36	In teens	No	Syncope in teens	QTc = 450, VPB 1
2-1M	E138K *de novo*	5.5	*In utero* (arrhythmia)	Yes (1 y)	Asymptomatic	QTc = 400 QTUc = 540, VPBs 63, nsVT(–)
3-1M	T75M	13	12 (PP)	Yes (12 y)	Arrhythmia, syncope, after ICD asymptomatic	QTc = 445, QTUc = 640, VPBs 40,000, nsBDT 604
3-2F	T75M	37	19, arrhythmia	No	Survived SCD,ICD at age 33 y	Data unavailable
4-1F	D71V	16	12, arrhythmia	No	Asymptomatic	QTc = 380, QTUc = 650, VPBs 2600, BVT frequent
4-2M	D71V	44	15, (PP)	Yes (15 y)	Asymptomatic	QTc = 470 QTUc = 650, VPBs 56, nsVT(–)
5-1M	T309I	18	13, cardiac	Yes (13.5 y)	Cardiac arrest/ICD (13 y)	QTc = 350, QTUc = 580, VPBs 5% of TDB
5-2F	T309I	40	Asymptomatic	No	Asymptomatic	QTc = 460, QTU = 660
5-3F	T309I	20	10 cardiac	No	Syncope, ICD (10 y)	QTc = 400, QTUc = 640, VPBs 4.5% of TDB
5-4F	T309I	65	No data	No	Arrhythmia	Not available
6-1F	R82W	17	7, arrhythmia	No	Syncope/ICD at 14 y	QTc = 380, QTUc = 610, VPBs 15,290, nsVT 40
7-1F	R82Q	15	12, arrhythmia	No	Syncope/ICD at 12 y	QTc = 430 QTUc = 700, VPBs 15% of TDB, sporadic nsBVT,
7-2M	R82Q	40	Teens, arrhythmia	No	Syncope in teens	QTc = 460 during sotalol therapy for Wolff–Parkinson–White syndrome
8-1F	G52V *de novo*	13.5	7 (PP)	Yes	Asymptomatic, long QT during arechin treatment	QTc = 450, QTUc = 640, VPBs 6988, nsBVT 10

Age expressed in years (y). Dx, diagnosis; PP, periodic paralysis; ECG, electrocardiography; ICD, implantable cardioverter-defibrillator; VPB, ventricular premature beat; BVT, bidirectional ventricular tachycardia; SCD, sudden cardiac death.

tests were performed. PP was diagnosed based on a history of documented flaccid paralysis episodes or an abnormal result on an electrophysiological long exercise test, as described by McManis *et al.*[8] All subjects underwent standard 12-lead electrocardiography (ECG) and ambulatory 24-hour Holter monitoring, which was performed during normal activity with 3-channel digitized recorders (Lifecard CF; Sentinel, USA). An evaluation of heart rate and presence of ventricular and supraventricular arrhythmias was performed (Impresario; Sentinel). Special attention was paid to the presence of ventricular premature beats (VPBs), ventricular couplets, and ventricular tachycardia (VT), especially when bidirectional (BVT) or polymorphic. Diagnosis of ventricular arrhythmias followed ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.[9]

During ECG and 24-hour Holter analysis, QT and QTc intervals were assessed with the Bazett formula. When a distinct U wave was present, QTU and corrected QTU (QTUc) intervals were also measured. According to current standards of ECG assessment, a QTc interval $\geq$450 ms in males and $\geq$460 ms in females is regarded as abnormal.[10] In all subjects, significant structural heart abnormalities were excluded with transthoracic echocardiography.

DNA Mutation Analysis. Genomic DNA was isolated from leukocyte nuclei using a standard procedure. Family numbers 1–5 were tested by L.P., numbers and 6 and 7 by R.P., and number 8 by K.Sz. Genetic screening for *KCNJ2* was performed by polymerase chain reaction and sequencing as reported previously.[1]

RESULTS

Table 1 lists the clinical findings and mutations of the ATS patients studied. Eight different *KCNJ2* mutations were found, and 3 of them are novel: c.155G>T (G52V); c.412G>A (E138K); and c.436G>C (G146R). They were considered causal

for ATS, because they were not found in the dbSNP and National Heart, Lung, and Blood Institute (NHLBI) Exome Sequencing Project databases, and they segregated by clinical phenotype in the tested families.

In 5 families we were able to document ATS in more than 1 family member (Table 1). There were 2 *de-novo* mutations, including a boy with a severe ATS phenotype (see case description below). In 1 family, the mother, with a history of cardiac arrhythmia, was not available for testing. In the probands, the time from first symptom to ATS diagnosis ranged from 1 to 10 years (mean 4.7 years). The testing led to ATS diagnosis in the remaining family members.

Case Description. The boy (patient 2-1) with an E138K *de-novo* mutation had a severe, early-onset clinical presentation. He was first seen in the Neurology Department at the age of 5.5 years for a diagnosis of recurrent episodes of flaccid paralysis lasting from hours to 1 week. His psychomotor milestones were normal, and he started walking unsupported at age 11 months. PP episodes were observed since he was age 13 months; their frequency ranged from 4–6 per month to once every 2 months. During most episodes he was not able to stand or walk unsupported, but between episodes his muscle strength was normal. He had a history of cardiac dysrhythmia first observed on cardiac monitoring before and during labor. When he was age 2 years, arrhythmia was observed during treatment with an over-the-counter drug containing pseudoephedrine. His mother was treated for epilepsy in her childhood, but she did not have the *KCNJ2* mutation. Otherwise, his family history was not relevant. On admission he presented with short stature (103 cm, below the 3rd percentile for age), hypertelorism, small chin, clindactyly of the fifth toe, and syndactyly of the second and third toes. During hospitalization, a normokalemic periodic paralysis episode lasting 1 day was observed. During this episode the boy could not ambulate. A McManis test performed during an interictal period demonstrated abnormal muscle membrane excitability after exercise, with a 58.6% decrement in compound muscle action potential amplitude after exercise, further confirming the diagnosis. This patient's cardiac abnormalities are presented in Table 1.

Periodic Paralysis. PP episodes were observed in 7 patients from 6 kinships, with 5 of them male. Eight female patients had an isolated cardiac phenotype. Only 1 patient presented with no family history of skeletal muscle involvement (the girl's mother is affected with arrhythmia by history). PP episodes were normokalemic in all families studied; only 1 subject (4-2) was documented to have both normo- and hypokalemic PP. Episodes lasted from 1 hour to over 1 week, always with marked improvement. Only 1 patient (1-1) had residual weakness between episodes. In all patients affected with PP, treatment with acetazolamide led to subjective improvement in paralysis severity and duration, but none became PP free.

Cardiac Manifestations. ***QTc Interval and U Wave.*** A normal QTc interval was present in 10 of 13 (76.9%) subjects, whereas a prolonged QTc interval was present in only 3, in 1 of whom it was recorded during sotatol therapy administered due to previously diagnosed typical Wolff–Parkinson–White syndrome (QTc 460 ms). This patient refused electrophysiological study. After the ATS diagnosis, sotalol therapy was continued, and no significant arrhythmia was observed. In another fully asymptomatic 15-year-old boy, the QTc was 470 ms, and no significant ventricular arrhythmia was found during Holter monitoring. In the third case, an asymptomatic female, the QTc was 460 ms. Prominent U waves were observed in 11 of 13 (84.6%) subjects.

Ventricular Arrhythmia. No, or insignificant ventricular arrhythmia, defined by sporadic VPBs only, was recorded in 4 of 12 patients in whom Holter monitoring was performed. The most frequent form of complex ventricular arrhythmia was BVT or bidirectional couplets, detected in 6 of 12 patients. Monomorphic, non-sustained VT, or frequent VPBs without BVT, were found in 2 patients only. All patients with ventricular arrhythmias received β blockers, most frequently bisoprolol.

Two of 15 (13%) patients survived cardiac arrest, with subsequent implantable cardioverter-defibrillator (ICD) utilized for secondary prevention. An ICD was also implanted in another 4 patients for primary sudden cardiac death (SCD) prevention. All patients had recurrent syncope and episodes of BVT with Holter monitoring. Altogether, an ICD was implanted in 40% of patients. In all, QTc measurements were within the normal range (Table 1). In addition, as mentioned in the case description, arrhythmia was diagnosed *in utero*, but no complex arrhythmia was observed subsequently; this patient is currently asymptomatic. Only 3 (25%) of 12 patients are clinically and electrocardiographically (Holter monitoring) asymptomatic.

Dysmorphic features were seen in all of our subjects. Mild hypertelorism and a small, triangular chin was observed in all probands and mutation carriers. A severely short stature was seen in patient 2-1, and a cleft palate was observed in patient 1-1. Most had clindactyly/syndactyly. None of the

subjects had congenital heart anomalies or renal malformations.

DISCUSSION

To date, over 40 different mutations and 3 small deletions of *KCNJ2* have been reported. There were 8 different heterozygous *KCNJ2* mutations in our study. Five were reported previously: c.224C>T (T75M)[11,12]; c.212A>T (D71V)[1]; c.926C>T (T309I)[13]; c.244C>T (R82W)[14]; and c.245G>A (R82Q).[12] We identified 3 novel *KCNJ2* mutations: c.155G>T (G52V); c.412G>A (E138K); and c.436G>C (G146R), including 2 *de-novo* mutations. They were found in probands who expressed all 3 typical ATS clinical features: dysmorphia; normokalemic PP; and cardiac arrhythmia.[1,3,4,15] The E138K mutation caused a severe phenotype with asymptomatic arrhythmia *in utero*, a finding not previously reported in ATS. In the remaining 2 probands with novel mutations, PP was a dominant clinical feature, although subclinical arrhythmia was also present. The patient with the T309I mutation had a history of aborted cardiac arrest at age 13 years and a family history suggestive of SCD in a maternal uncle. In all but 1 family, 3 ATS features could be documented, with variability between and within families.[6,15] We observed PP attacks in 20% of females and 80% of males. A history of syncope or cardiac arrest occurred in 50% of females and 60% of males. In a previously reported large kindred with the R67W mutation, ventricular arrhythmias segregated with females (13 of 16 studied, 81%), whereas PP was observed in 10 of 25 (40%) male mutation carriers.[16] Reduced expressivity of mutations and lower attack frequency in women than in men with PP is also a feature of hypokalemic PP caused by *CACNA1S* and *SCN4A* mutations.[17] The exact mechanism of such gender specificity of PP episodes in ATS has not been elucidated.

Studies have shown that estrogen exerts a strong effect on Kv4.3 potassium channel expression.[18] Hormonal influences on Kir2.1 function mediated by a corticoid signaling pathway were also demonstrated.[19] We were not able to perform physiological studies to identify the nature of the alteration in channel function caused by the novel *KCJ2* mutations. Previous studies demonstrated that the ATS phenotype may occur as a result of a defect in trafficking and conductance of the inward-rectifier K^+ channel.[20] Dysfunction of the skeletal muscle inward-rectifier K^+ channels also leads to depolarization-induced paralysis in hypokalemic periodic paralysis caused by calcium channel mutations (*CACNL1A3*) and in thyrotoxic PP.[21,22] In *CACNL1A3* mutations the paradoxical depolarization in low K^+ is not prevented by the CaV1.1 blocker nitrendipine. The membrane current–voltage relationship mostly reflects the activity of K^+ channels.[22] The cardiac phenotype was highly variable in our patients. The clinical spectrum included clinically and electrocardiographically asymptomatic subjects (25% of observed cases) and also 2 SCD survivors. Although only a few cases of sudden cardiac death in ATS have been reported previously,[23] a 45-year-old uncle of our proband had fatal SCD. ICDs were implanted in 2 SCD survivors and in another 4 of our patients with recurrent syncope and complex ventricular arrhythmia for primary SCD prevention.

Although ATS is classified as a long QT7 syndrome (LQT7),[2] our data are consistent with previous observations and showed a normal QTc interval in 76% of patients studied. However, in accordance with a published ECG study, which reported no QT prolongation but an abnormal T–U-wave pattern,[24] we observed prominent U waves in standard ECGs of 84% of patients. Importantly, the majority of patients (approximately 75%) had ventricular arrhythmia, which corresponds to recent studies reporting ventricular arrhythmia in 80% of cases.[25] Interestingly, BVT was a typical complex arrhythmia in our subjects.

In conclusion, the reported *KCNJ2* mutations demonstrated a variable phenotype. We found dysmorphic features in all of our patients, a high penetrance of PP in males, and polymorphic ventricular tachycardia with a risk of SCD.

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